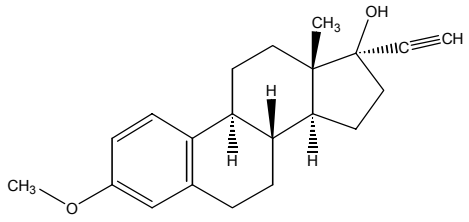
ESTROGENS (NOT CONJUGATED)

MESTRANOL
CAS No. 72-33-3
First Listed in the *Fifth Annual Report on Carcinogens*



CARCINOGENICITY

Mestranol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC V.6, 1974; IARC V.21, 1979; IARC S.4, 1982; IARC S.7, 1987). When administered alone orally to mice, mestranol increased the incidences of pituitary and malignant mammary tumors. Mestranol also induced an increased incidence of malignant mammary tumors in female rats when administered orally (IARC V.6, 1974).

There are a number of studies involving the oral administration of mestranol in combination with progestins. In these studies, mice developed pituitary tumors, vaginal and cervical squamous cell carcinomas, and mammary tumors. Rats with similar mixed exposure developed benign liver tumors and malignant mammary tumors. Dogs developed mammary cancers after mixed exposure to progestins (IARC V.6, 1974; IARC V.21, 1979; IARC S.4, 1982). Subcutaneous injection of a combination of mestranol and progestins induced cervical cancers and pituitary tumors in mice (IARC S.4, 1982).

There is inadequate evidence for the carcinogenicity of mestranol in humans (IARC V.6, 1974; IARC V.21, 1979; IARC S.4, 1982). There is sufficient evidence for the carcinogenicity of steroidal estrogens in humans (IARC S.7, 1987). Case reports and epidemiological studies of humans given mestranol alone were not available. However, the use of oral contraceptives containing mestranol in combination with progestins is associated with an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease, endometrial cancer, and ovarian cancer. Epidemiologic studies also strongly suggest that the administration of estrogens alone is associated with an increased incidence of endometrial carcinoma, and there is no evidence that mestranol is different from other estrogens in this respect. An IARC Working Group concluded that in the absence of adequate data in humans, it is reasonable to regard mestranol as if it presents a carcinogenic risk to humans (IARC V.21, 1979).

PROPERTIES

Mestranol is a white crystalline solid. It is practically insoluble in water; slightly soluble in methanol; and soluble in ethanol, acetone, diethyl ether, chloroform, and dioxane. Mestranol is available in the United States as a USP-grade containing 97-102% mestranol on a dried basis.

USE

The most widespread use of mestranol is in oral contraceptives where it is used as the estrogen in combination therapy, sequential therapy, or the estrogen tablet alone (IARC V.6, 1974). It also is used in combination with a progestin to treat such conditions as endometriosis and amenorrhea (IARC V.21, 1979). Mestranol is not known to be used in veterinary medicine (IARC V.6, 1974).

PRODUCTION

The USITC and the 1979 TSCA Inventory do not identify any producers or production volumes for mestranol. The 1998 Chemical Buyers Directory names one supplier of the compound (Tilton, 1997). The 1984 Chem Sources USA directory listed one producer and seven suppliers of mestranol (Chem Sources, 1984). In 1983, imports of mestranol totaled 22 lb (USITCa, 1984). IARC reported in 1979 that no commercial production of mestranol existed in the United States (IARC V.21, 1979). In 1974, total U.S. sales of mestranol for use in human medicine were estimated to be < 220 lb annually (IARC V.6, 1974).

EXPOSURE

The primary routes of potential human exposure to mestranol are ingestion, dermal contact, and inhalation. Potential consumer exposure may occur through ingestion of pharmaceuticals containing mestranol. Up to 1% mestranol has been detected in norethynodrel (as normally manufactured). Potential occupational exposure to mestranol may occur through inhalation and dermal contact. In a study carried out in a plant producing oral contraceptives, mestranol was found in various sectors of the working environment at levels ranging from 0.06 to 8.61 $\mu g/m^3$, and on wipe samples at levels of 0.003 to 2.05 $\mu g/cm^2$ (IARC V.21, 1979). A joint investigation of an oral contraceptive plant, conducted by NIOSH and CDC, found evidence of hyperestrogenism among male and female workers. Blood tests showed 60% higher elevations of estrogens among employees who handled the powdered product; air samples of estrogen and progesterone varied widely (Drug Cosmet. Ind., 1977). Another source of potential human exposure to mestranol is the residue in foliage, soil, and water samples.

REGULATIONS

EPA has proposed regulating mestranol as a hazardous constituent of waste under the Resource Conservation and Recovery Act (RCRA). FDA regulates mestranol under the Food, Drug, and Cosmetic Act (FD&CA) as a prescription drug approved for human use. FDA has ruled that estrogens for general use must carry patient and physician warning labels concerning use, risks, and contraindications. This ruling on warning labels has been extended to all oral contraceptives. OSHA regulates mestranol under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table B-62.